Abstract

Brain activity is characterized by oscillatory activity that spans at least two orders of magnitude. Previous investigations of the spatiotemporal dynamics of this wide range of oscillatory behavior has led to the concept that long-range intercortical interactions are expressed in low-frequency patterns while higher frequencies reflect more local intracortical connectivity. This inverse relationship between frequency and spatial coherence is seen as one of a small number of nearly universal rules governing brain activity. While there is substantial evidence for this proposition, there are surprisingly few direct, quantitative investigations of this phenomenon, especially in human cortex. To more completely characterize the spatial characteristics of ongoing brain activity, we investigated the coherence in different brain states—awake and sleep, at different frequencies, and with respect to a wide range of distances using standard pial surface macroelectrode arrays (1 cm spacing in an 8x8 cm grid), mesogrids (5 mm spacing), microgrids (1 mm spacing), and microelectrode arrays (400 micron spacing in 4x4mm arrays). As expected, we found that correlations and coherence decreases as a function of increasing interelectrode distance and as a function of frequency. We observed a robust linear relationship up until 1 cm; for distances 1 cm and greater, the relationship was largely non-linear. This relationship was not strongly affected by specific cortical lobe, nor was the overall coherence significantly different between awake and asleep states. These data are congruent with the overall notion that frequency and spatial relationships are inversely related with faster frequencies being more focal and provides an important quantitative assessment of that relationship with implications for the spatial scale of neural processing and recordings.

Keywords: Electrocorticography, Coherence analysis, Correlation analysis, Topography

1 Introduction

Neuronal oscillations are ubiquitous across the human cortex and are believed to orchestrate the interactions of complex neuronal assemblies through transient coupling across multiple temporal and spatial scales[25]. This coupling between and across different frequency bands...
is hypothesized to allow for the integration and encoding of brain states and information[24, 21, 15, 5, 22, 23, 24, 12]. The resulting cortical functional networks are thought to underlie multiple cognitive processes [13, 14, 15, 21] and are also associated with a wide range of different states ranging from low frequencies during sleep[4] to high frequencies implicated in higher order cognitive activity[48, 16, 26, 27]. Moreover, these same oscillations and the related networks have been found to be disrupted in many cortical diseases [27, 17, 28]. Thus, there is substantial evidence that oscillations function in important and unique ways. There are many research groups exploring individual aspects of activity for answers. The major question for the broader neuroscience community, however, is how spontaneous neural activity is modulated across spatial and temporal scales, culminating in organized network activity. A now longstanding meme in the neuroscience community is that there is an inverse relationship between the frequency of a neural oscillation and the space over which it is coherent. A number of studies over the past decades have explored this either directly or indirectly on a single scale[5, 29, 3, 30, 32, 18, 19, 6, 7, 8, 9, 10]. These studies have confirmed the inverse relationship between frequency and spatial coherence[33]. For example, Arieli et al.[34] used electrophysiological and optical techniques to show that patterns of intrinsic electrical activity in the visual cortex of anesthetized cats is coordinated at spatial scales up to several millimeters [49].

While the literature has provided evidence for the hypothesis that there is an inverse relationship between frequency and the spatial extent of coherence, there has been little quantification of the nature of this relationship in human cortex, in steady states and across a full range of scales from sub-millimeter to centimeter. In this work, we integrated electrical recordings from intracranial electrodes (Fig. 1) implanted in epilepsy patients at multiple scales with impressive resolution (as seen in Fig. 6). This was done in attempt to bridge the levels underlying local and long-range interactions. We studied these interactions using clinical and research electrode, brain monitoring tools suited to investigate the microscopic, mesoscopic, and macroscopic features of the brain. Such a systematic characterization is fundamental to understanding the specific and shared aspects of the brain across scales, building realistic models of neural activity and, ultimately, developing new biomarkers and therapeutic interventions. Furthermore, the issue is of significant importance in the design of advanced recording systems. Future arrays will have a higher electrode number and density which will be better able to harness the neurons, networks, and noise altogether, giving insight into their organizing principles.

2 Methods

2.1 Patients

Data from a total of 31 patients with pharmaco- resistant epilepsy (age at surgery ranged from 19-52 with the median age being 29) who underwent invasive intracranial electroencephalography (iEEG) as a necessary component of their clinical care were included in this study. The decision to implant electrodes, macroelectrode placement, duration of visit, and resective surgery were based purely on the clinicians judgment, without regard for this research. Patients implanted with microelectrode arrays were approached to participate in research studies only after the determination was made that they should undergo surgery. The analysis of this data and the implantation of microelectrodes was performed under the
auspices of a fully informed consent process approved by the IRB in accordance with the National Institutes of Health guidelines and the Declaration of Helsinki.

2.2 Data Acquisition

Data from four different types of electrodes were analyzed (Fig. 1)- macroelectrodes, meso-electrodes, and two microelectrode varieties. Macroelectrodes (subdural arrays, Ad-Tech Medical Instrument Corporation, Racine Wisconsin or PMT (PMT Corporation (Chanhassen, MN))) consisted of two-dimensional surface arrays resting on the pia. These are standard electrode arrays used for clinical purposes. A distant common reference consisting of a strip of electrodes facing the dura, was used for these grids of electrodes. What we are terming mesogrids were situated in unique configurations with 5 mm interelectrode spacing. Microgrids (Ad-Tech Medical Instrument Corporation or PMT Corporation)) were coupled with the macroelectrode grid laying on the pia. Microgrids consist of multiple 1 mm spaced, 40-um diameter contacts made of platinum/iridium (PtIr) wires with the end cut flush with a silastic membrane (the same membrane supporting the macroelectrodes, [2, 3]). Finally, the NeuroPort array or multi-electrode array (MEA) (BlackRock Microsystems, Inc., Salt Lake City, Utah) was used. This array covers 4 mm x 4mm of cortex with 96 electrodes (400 m interelectrode spacing, 1 or 1.5 mm electrode length). In total, data from 21 macroelectrodes, 4 mesoelectrodes, 7 microgrids, and 6 multielectrode array arrays were analyzed. In 10 of those patients we were able to record simultaneously from a combination of electrode arrays.

Recordings of macrogrid electrodes were performed with standard clinical recording equipment (Xltek, a subsidiary of Natus Medical), sampled at 500 Hz. Microelectrodes were recorded using a BlackRock Cerebus system recording at 32 Hz. Continuous epochs of baseline data (all approximately 3 minutes in length) were determined to represent either awake or sleep (stage II or III) by an experienced electroencephalographer (SSC). This data was selected to avoid major artifacts such as those induced by large movements. Channels with substantial noise or poor recording and substantial epileptiform activity were excluded from analysis. A common montage was used to process the ECoG and microgrid data. (A bipolar reference was also used but the results are being held for a later version of this manuscript.)

2.3 Anatomical Reconstructions

Three-dimensional (3D) models were rendered from the structural MRI of each patient using FreeSurfer [35] and then coregistered with the postoperative computed tomography (CT), detailing the placement of the intracranial electrodes. For this analysis, each electrode was picked manually and projected onto the 3D surface (see [36] for details).

2.4 Data analysis

To characterize the four different types of electrode arrays with their varying spatial resolutions, we used linear functional connectivity measures. (We also used nonlinear connectivity measures, however this analysis will be part of a later version of this manuscript).
2.4.1 Correlation

A standard univariate correlation measure (MATLAB) was used to characterize the data for both awake and sleep periods for all possible pairs of a given array (Fig. 2). Additionally, we measured coherence as a frequency-dependent statistical correlation measure. In order to measure the coherence in activity between two locations we use the bivariate cross-correlation, computed in seven frequency bands, extending the classical Berger Bands (1-25 Hz) (Berger 1929, Gloor 1969, 1975): 3 to 4 Hz ([delta]), 4 to 7 Hz ([theta]), 7 to 13 Hz ([alpha]), 13 to 16 Hz (low [beta]), 16 to 30 Hz (high [beta]), 30 to 55 Hz (low [gamma]), and 65 to 100 Hz (high [gamma]).

2.4.2 Coherence

Signal coherence was calculated between pairs of channels within each grid. For macro-grids, micro-grids, and Multielectrode arrays, all pairs were compared; for meso-grids, certain pairs were excluded for high inter-electrode distance. Coherence results were then binned into frequency bands and inter-electrode distance. Summary statistics for coherence were calculated within frequency bands and analyzed relative to inter-electrode distance.

3 Results

In this study, we recorded from 2400 active electrodes distributed over four differing spatiotemporal scales- the greatest area in contact with brain tissue being 4\pi mm, while the smallest area is a thirteenth of that number.

3.1 Correlation and correlation decrease as a function of interelectrode distance.

We used the correlation and coherence functions to characterize the statistical and spatial properties pervasive in this high dimensional set. In keeping with previous studies, as described above, our investigation found that both correlation and coherence fall off with distance (Fig. 2, 3). To more completely quantify this relationship we examined the maximum cortical distance, the correlation length, at which signals remained 90% synchronous, at which point the strength of association drops significantly. Here, we observed that long range connections (as in the macro and meso electrodes) tended to fall off at about 4 cm, while the local, small-scale connections were coherent until 10 mm. Our observations suggest that linear and non-linear correlation of oscillations are associated with the spatial scale. More specifically, when recorded with the microelectrode arrays, the decay appears to be much more rapid, approximating a linear diminution over space. A salient finding was the coherence decay shape is unique for each scale. Taken together, we can see an elegant example of the power-scaling relationship with the power-law decay of coherence with distance.

3.2 Coherence rapidly declines in the higher frequency domain.

As expected, higher frequency activity showed a more precipitous decline with distance than did the slower frequency bands. This was most pronounced in the macroelectrode plot.
As expected, the spectral profile of global networks is dominated by low frequency activity. Thus, the lowest frequency bands were the most correlated across large distances, as much as 3-4 cm. In contrast to the widespread lower frequencies, we can see a distinct spectral profile for local networks. The gamma band correlation had fallen to .35 within 5 cm. With decreased inter-electrode distance, the spectral representation improved with all bands well correlated until roughly 3-4 mm.

3.2.1 Invariance of coherence with respect to brain state

It has been shown that particular states and frequency domains have low coherence, suggesting weakly or uncorrelated activity, however, the two brain states under investigation, wakefulness and slow-wave sleep, demonstrated no consistent or marked characteristics in coherence at any distance. In fact, the spatial-frequency coherence relationship was actually quite similar between the two states. Correlation and coherence are generally higher during sleep (consistent with [49]).

3.2.2 Coherence with respect to regions

In an effort to relate synchronous patterns to cortical anatomy, we performed several comparisons. Our first topographical analysis of the cortex observed the interaction between two electrodes when 1.) laying on the same gyri and 2.) across sulci, however this lent no convincing differential and was not significant. Additionally, it was hypothesized that electrode correlation over a large sulcus like the sylvian fissure might be more impressive. However, after analysis, this was not the case; again, the results were unremarkable. After measuring the associations of electrode duos, we compared the correlation is specific regions or lobes of the brain. Still, hemispheric comparison ultimately shows invariance, possibly suggesting that specific correlated behavior may not be attributed to certain brain regions. Ultimately, coherence did not seem to vary according to cortical location. These results may speak more to the makeup of the gyri and sulci, and less to the underlying connectivity.

3.3 Microscale activity behaves differently than the macroscale

The brain contains multiple overlapping patterns of activity ranging over 4 orders of magnitude. Multiscale recordings are the only way appreciate this complexity. With the different spatial and temporal resolutions offered by the hardware, we found non random, non-redundant structure in the microdomains (Fig 3). We see this in the differing dissipating dynamics that emerge at the different levels. That is, the magnitude of downward trend varies. We know that the power law is a universal phenomena of the brain, but the power-law avalanche is not identical or necessarily resonant across space. More specifically, the networks seen by the MEA are unique as compared to the lower resolution electrodes. We know this by the linear shape of the MEA correlation over distance, which indicates that those MEA networks have higher thresholds and thus are more correlated. In such analyses, it can be helpful to consider extreme cases to shed light on possible generators beneath the cortex. If the activity at each electrode were generated independently, we would expect a vertical line (slope of zero). At the other end of the spectrum, if activity across the brain was collectively driven equally across all electrodes, we would observe a horizontal relationship (slope of zero).
4 Discussion

Unlike other studies on this topic, this study, initiated in 2011 (first presented in 2012, see Appendix A) was the first to incorporate and integrate data from the macro-, meso-, and micro- scales. Overall, there was a clear decrement in coherence with distance, and the decrement was faster for higher frequencies. This relationship was not strongly impacted by specific cortical lobe, nor was the overall coherence significantly different between the two endogenous brain states, awake and asleep. These data are congruent with the overall notion that frequency and spatial relationships are inversely related with faster frequencies being more focal.

In this study, we have quantitatively investigated the spatial and temporal dynamics of spontaneous oscillatory activity occurring during the steady state awake and sleep periods. Using multiscale neurophysiological techniques with micro-, meso-, and macro- electrode arrays we found that the degree to which activity is related varies with distance and frequency. As expected, at greater distances there is substantially less correlation or coherence between any two structures. This is also true as electrode size increases. Activity within the microdomains is tightly correlated, and we observed the power law extend and almost plateau at great distances. A battery of connectivity measures allowed us to really get a sense for the scales. This drop in correlation is steep for high frequency activity. Perhaps most interestingly is the shape of the relationship, suggesting that global and local networks reflect distinct brain frequencies.

Historically, the field has studied the brain in elementary parts on a single scale because resolving scales is problematic. The human brain mapping project has catalyzed the transition towards an integrated representation, taking into account the physical context and environment of the brain. The only way to approach this fundamental challenge in brain research- how does the brain do what it does- necessitates a more holistic strategy, involving multi-scale study. Fortunately, this kind of data is accessible using multi-scale electrodes and speaks to the merit of multi-modal recordings and their ability to overcome the nettling limitations of a single scale, improving overall spatial and temporal resolution. This was an obvious key difference in our experimentation.

In agreement with previous studies, we observed the importance of slow oscillations in large network activity as well as the restricted spatial involvement of fast oscillations present focally. We did not observe coherent gamma activity at 5mm or at any greater distance, in line with the literature [1]. The underlying neural structures that enforce this relationship remain unclear. On the one hand, increased connectivity between spatially close and functionally related units has been observed in structural networks across spatial scales ranging from microns to centimeters [24, 37, 39, 38]. Similarly, evaluation of human fMRI functional networks has demonstrated increased functional connectivity between anatomically proximal regions [43, 40, 44]. This modular network architecture has been proposed to both increase computational efficiency and decrease energy costs by organizing highly clustered modules that can be linked by few long distance connections [41, 42] in a small world network fashion. However, how this underlying structural pattern can lead to a coordination of activity that is different based on frequency is unclear.
4.1 Limitations

We observed no significant differences in coherence for brain state, brain region, or across the sylvian fissure, which can be resolved in potentially two ways. The first is by taking the variability of the patient data into account, specifically, the heterogeneity of electrode placement or the sparse-sampling problem, and the second - the volume of brain that can be effectively sampled over gyri. To help address these concerns, we began excluding any channels implicated in seizures in addition to noisy channels. However, we found that this had no significant difference. One of the main limitations has been resolving the volume conduction properties of brain tissue. In a future stage of our study, we plan to address the practical and prevalent trap of volume conduction and its subsequent spurious interactions by using a bipolar reference, after testing monopolar, common, and average reference alternatives before. In addition, we use a novel method for volume conduction correction using imaginary coherence.

5 Conclusions

In the end, we used a strict set of inclusion/exclusion criteria to identify artifact-free ECoG data. This is consistent with similar studies, however. (agrees with [45]). Consideration should be given to the impact of electrode features on electrocorticography. The spatial resolution and correlation of electrical activity at the cortical surface is limited by the size of each electrode contact as well as the interelectrode spacing. Optimizing electrode design could improve our knowledge of the spatial networks of the brain. Further work developing other measures of cooperativity could extend and address critical questions about local interactions and large-scale dynamics. This work compliments and extends our knowledge of oscillations. The hope is that detailed physiological data will offer a fresh perspective on how hierarchical oscillatory activity may be constructed as networks across the cortex, which can inform ongoing work in seizure physiology and the next generation of computational models of the brain.

6 Acknowledgements

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7 Figures and Tables
Figure 1: Electrode schematic showing spatial relationships A) Relationship between Electrodes at different scales.
Figure 2: Correlation as a function of distance. Grand average correlation in sleep and awake states (from top to bottom: macrogrid, mesogrid, microgrid, and utah array)
Figure 3: (A) Comparison of correlation and coherence of spontaneous oscillations at different spatiotemporal scales. Simultaneous ECoG recordings of LFPs and macroelectrode (top row or panel?) and microelectrode arrays (bottom row) are shown. (B) Comparison of correlation and coherence across electrodes results for Patient B in the awake state including both a macrogrid and a multielectrode array array (MEA).
Figure 4: Grand average spatial correlation values for the three different electrode datasets (X patients for macrogrid, Y patients for microgrid, Z patients for multielectrode array) during the awake and sleep states. This graph shows clearly our result that high correlation is prevalent at the finer scales.

Figure 5: Coherence of raw LFP signal shows frequency-dependence. Time series of coherence data over each of the seven frequency bands for each of the electrode types in both awake and sleep states. Top panel, macrogrid, awake and sleep. Second panel, .. Third panel. Each color corresponds to one of the 7 chosen frequency bands.
Figure 6: Schematic depicting the various methods used in study the brain with their associated spatial and temporal resolutions.
Appendix A: Poster Presentations of Project

A.1 Society for Neuroscience, 2012

Poster Number 746.05/D28

Presentation Title Spatiotemporal behavior of oscillatory activity in human cortex

Abstract Previous investigations of the spatiotemporal dynamics of oscillatory behavior in the brain has lead to the concept that slower activity has coherence spanning over a wider area than that of higher frequency activity. This is seen as one of a small number of nearly universal rules which dictates activity in cortical and subcortical structures. There is substantial evidence for this proposition in the literature but surprisingly few direct investigations, especially in human cortex. Furthermore, the majority of investigations of this issue have focused on relatively large distances. For this reason we investigated the coherence in different brain states- awake and sleep- at different frequencies with respect to distance using both standard pial surface macroelectrode arrays (1 cm spacing in a 8x8 cm grid), macroelectrode arrays which penetrate the brain parenchyma and both microgrid (1 mm spacing) and NeuroPort microelectrode arrays (400 micron spacing in 4x4mm arrays). As expected, we found that coherence decreases as a function of increasing interelectrode distance; for both electrode types there was a decrement in coherence over space. For the macrogrids and distances greater than 1 cm, the relationship was largely non-linear. In contrast, at the microscale the drop in coherence was linear. This relationship was not strongly affected by state, nor was the overall coherence significantly different between awake and asleep states. The impact of frequency on spatial relationship was variable from subject to subject but showed a trend toward more rapid declines in coherence in higher frequency bands. These data are congruent with the overall notion that frequency and spatial relationships are inversely related with faster frequencies being more focal.
Poster

Spatiotemporal Behavior of Oscillatory Activity in Human Cortex

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Abstract

The concept that diverse activity has coherence spanning over a wide range that of lower frequency activity is seen as one of the major roles of neural synchrony which makes activity in cortical and subcortical structures. Considering that the majority of investigations of these have focused on relatively large distances, we investigated the global and local influence in different brain states—alpha and slow—different frequencies with respect to distance using 4 different electrode types. These data are consistent with the overall notion that the frequency and spatial relationships are strongly associated with the frequency being more focal.

Methods

Our study currently includes 21 patients who underwent invasive intracranial electroencephalography (EEG).

- Analysis of four different types of electrodes (A-D):
  - Electrodes:
    - A: standard surface electrodes
    - B: electrodes inserted in depth electrodes
    - C: electrodes on standard subcortical areas
    - D: surface electrodes inserted in subcortical areas

- Both analyzed in standard EEG

- Coherence was computed in a narrow frequency band

- Analysis of different types of electrodes

- The closer you are, the more unique structure you are.

Conclusions

- Decrease in signal coherence with increasing interelectrode distance
  - Consistent at all electrode types, though rate of change varies
  - Frequency measurement specific
  - Fundamental nature of higher frequency
  - High-frequency signal independent of macroscopically
  - Brain state unique
  - Regional variations

Correlation appears to be state-dependent.
Abstract
Previous investigations of the spatiotemporal dynamics of oscillatory behavior in the brain has led to the concept that slower activity has coherence spanning a wider area than that of higher frequency activity. This is seen as one of a small number of nearly universal rules which dictates activity in cortical and subcortical structures. There is substantial evidence for this proposition in the literature but surprisingly few direct investigations, especially in human cortex. Furthermore, the majority of investigations of this issue have focused on relatively large distances. To more completely characterize the spatial characteristics of ongoing brain activity, we investigated the coherence in different brain states, awake and sleep, at different frequencies and with respect to a wide range of distances using both standard pial surface macroelectrode arrays (1 cm spacing), macroelectrode arrays which penetrate the brain parenchyma and both microgrid (1 mm spacing) and NeuroPort microelectrode arrays (400 micron spacing). As expected, we found that coherence decreases as a function of increasing interelectrode distance. For distances 1 cm and greater, the relationship was largely non-linear, and smaller gaps behave more linearly. This relationship was not strongly affected by recording location, nor was the overall coherence significantly different between awake and asleep states. The impact of frequency on spatial relationship was variable from subject to subject but showed a trend toward more rapid declines in coherence in higher frequency bands. These data are congruent with the overall notion that frequency and spatial relationships are inversely related with faster frequencies being more focal.
**Poster**

**MOTIVATION**

Clinical use of implantable electrode arrays has provided an occasion to not only record epileptic events, but intrinsic spontaneous brain behavior as well. A now longstanding meme in the neurosciences is that there is an inverse relationship between the frequency of a neural oscillation and the space over which it is coherent. This is seen in one of the many neural mass models which simulate activity in cortical and subcortical structures. There is surprisingly few direct investigations, especially in human cases. Furthermore, the majority of studies of this issue have focused on relatively large distances.

**METHODS**

We investigated the coherence in different brain states, awake and asleep, at different frequencies and with respect to a wide range of distances using both standard planar-surface macroelectrode arrays (1 cm spacing in a 3 x 3 cm grid) and both microgrid (1 mm spacing) and Neuropen multi-electrode arrays (500 micron spacing in 4x4mm arrays).

**CONCLUSIONS**

- Decrease in signal correlation with increasing interelectrode distance.
- Consistent in all electrode types, though rate of change varies.
- Frequency sensitivity and specificity.
- Focal nature of higher frequencies.
- Suggesting signal independence on microscale.
- Brain state invariance.
- Regional invariance.

**References:**


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**Figure 1.** Correlation of both the awake and slow states ranging from 40 microns to 10 cm. As expected, we found that coherence decreases as a function of increasing interelectrode distance. For distances 1 cm and greater, the relationship was largely non-linear but with smaller gaps between electrodes the relationship became more linear. This relationship was not strongly affected by recording location, but was the overall coherence significantly different between awake and asleep states.

**Figure 2.** The impact of frequency on spatial relationship was variable among subject but showed a trend toward more rapid depressions in coherence at higher frequency bands. Either measures of signal relationship showed... These data are congruent with the overall notion that frequency and spatial relationships are inversely related with higher frequencies having more focal.

**Figure 3.** It was hypothesized that electrode correlation over a large area like the sylvian fissure might be more impressive. Hemispheric comparisons in 4 patients with subarachnoid hemorrhage prominently shows invariance.
References


